Cardiovascular and Renal Drugs Advisory Committee

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Issues Affecting Interpretation of Efficacy

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Outline

- Assessing efficacy in non-inferiority and superiority trials
- Adequacy of warfarin management in ROCKET and potential impact on results
- Post treatment primary endpoint events in ROCKET and J-ROCKET
- Approval standard in 2011 for a drug to prevent stroke in patients with atrial fibrillation (AF)

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Analysis of Non-Inferiority and Superiority

- Analysis of the per-protocol population while on treatment was used to assess non-inferiority
  - Non-inferiority was declared
  - Robust finding supported by multiple supportive analyses
  - Impact of quality of warfarin management not considered in these analyses
- Analysis of the safety population while on treatment was used to assess superiority
  - This analysis indicated superiority but
  - ITT analyses (i.e., all patients randomized regardless of treatment status) failed to support superiority

ICH E9 – Statistical Principles for Clinical Trials

- Superiority analysis – ITT analysis is usually primary “apart from exceptional circumstances”
- Non-inferiority analysis – “per protocol” analysis is usually primary
- Agreement of ITT and “per-protocol” increases confidence in the trial’s results

ICH E10 – Choice of Control Group and Related Issues in Clinical Trials

"A finding of superiority in an active controlled trial is interpretable as true superiority only if the control is used in appropriate patients at an appropriate dose and schedule."

FDA Draft Non-inferiority Guidance (2010)

- Non-inferiority analysis – both the “as-treated” and ITT populations should be analyzed
- Superiority analysis – the primary analysis should be ITT because as-treated analyses are prone to bias from informative censoring

Overall Efficacy Findings

In ROCKET –

- None of the ITT analyses support superiority of rivaroxaban to warfarin
- As-treated and ITT analyses support non-inferiority of rivaroxaban to warfarin <u>as it was used in ROCKET</u>
- These analyses do not consider how the quality of warfarin administration might have affected the outcomes

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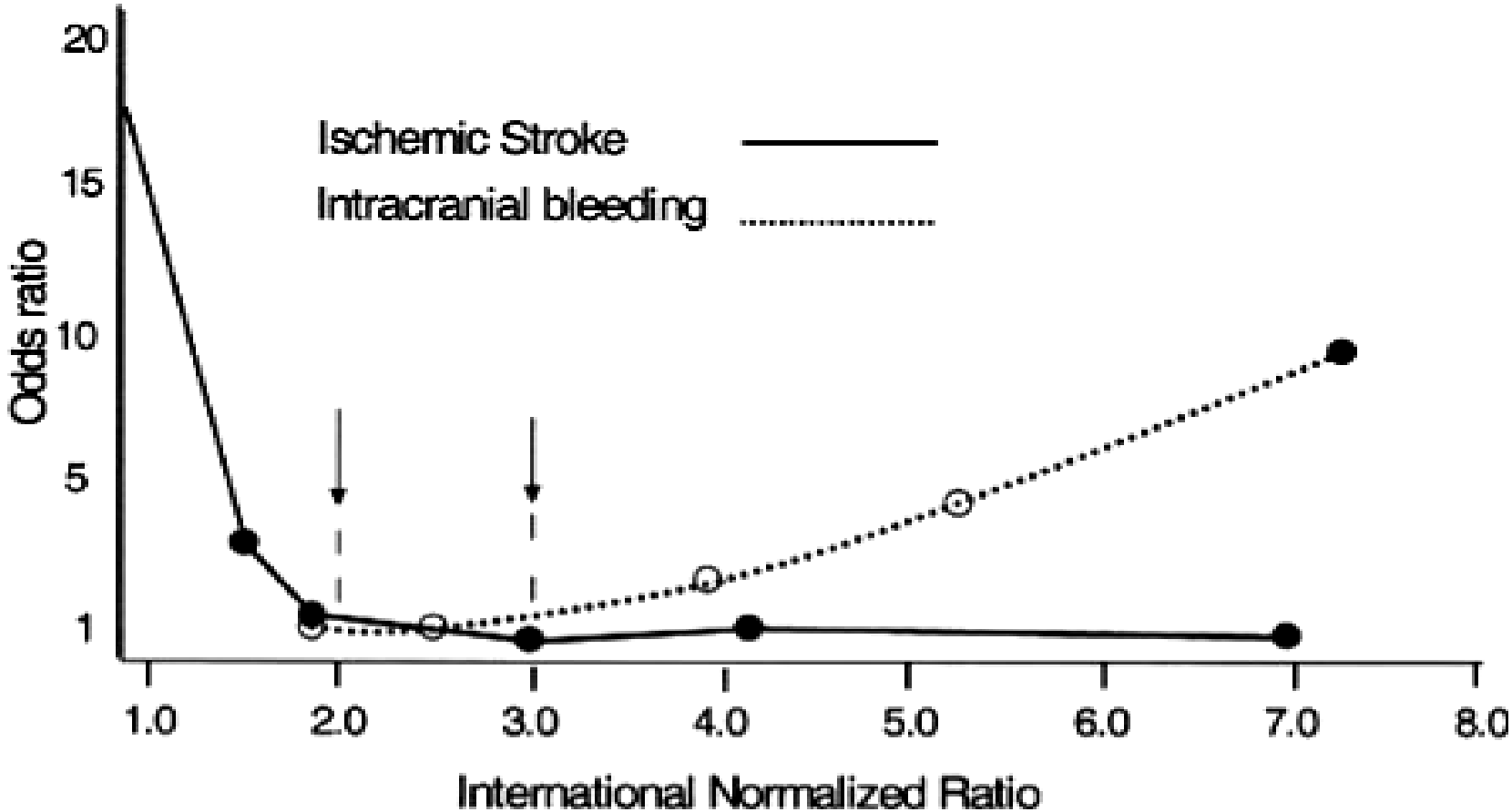
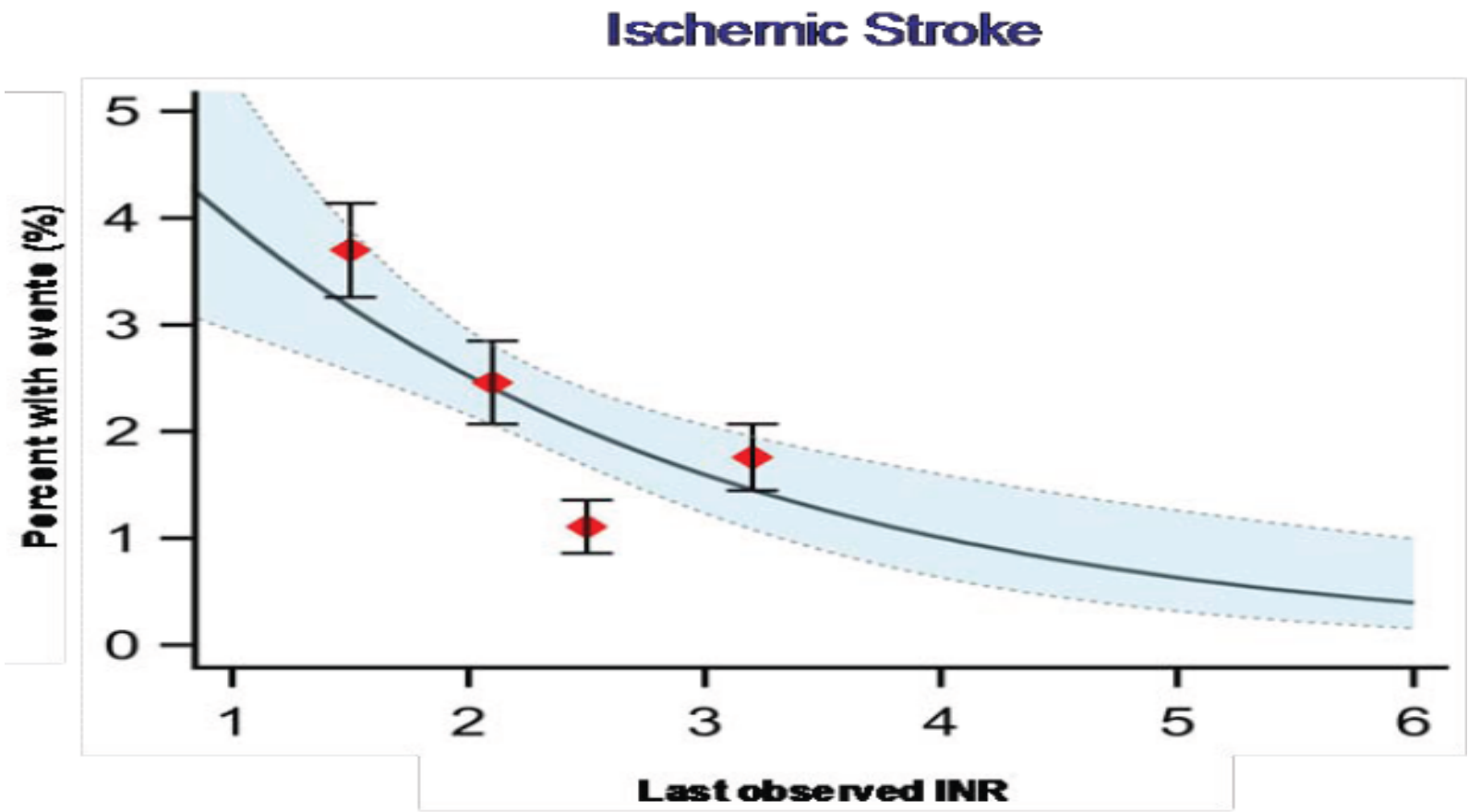
Stroke Rate vs INR in Patients with AF



Source: 2011 Focused Updates of ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation

ROCKET Warfarin Arm: Relationship of INR to Ischemic Stroke Rate



Management of INR in ROCKET

- Protocol specified a procedure for starting study drug in patients on VKA (vitamin K antagonist, e.g. warfarin) at baseline, but -
- Did not stipulate an algorithm for managing VKA dose

(Transition to VKA at the end of the study will be discussed later)

ROCKET – Percent Time in Various INR Ranges in Warfarin Arm

INR Range	Mean	Median
<1.5	8.5%	2.7%
1.5 - <1.8	10.4%	7.9%
1.8 - <2	10.3%	9.1%
2 – 3	**55.2%**	**57.8%**
>3 - 3.2	4.8%	4.0%
>3.2 - 5	9.9%	7.9%
>5	1.0%	0.0%

Stroke Risk Increased with INR Below 2.0

OR for Ischemic Stroke (vs INR of 2.0)	
INR	**Odds Ratio (95% CI)**
1.9	1.2 (1.2 - 1.3)
1.8	1.5 (1.4 - 1.7)
1.7	2.0 (1.6 - 2.4)
1.6	2.5 (1.9 - 3.3)
1.5	3.3 (2.4 - 4.6)
1.4	4.4 (2.9 - 6.6)

Source: Hylek EM et. al., NEJM 1996; 335:540-46.

OR for Ischemic Stroke (vs INR of 2.0)	
INR	**Odds Ratio (95% CI)**
1.8-1.9	1.25 (0.80 - 1.96)
1.4-1.7	3.72 (2.67 - 5.19)

Source: Singer DE et. al. Circ. Cardiovasc. Qual. Outcomes 2009:2:297-304

Mean INR Time in Therapeutic Range (TTR) in Recent Trials using Warfarin as Control

Trial	Mean TTR
ROCKET	55
ACTIVE W	64
AMADEUS	63
ARISTOTLE	62
EMBRACE AC	73
RELY	64
SPORTIF III	66
SPORTIF V	68

Site Mean INR TTR Quartiles in Warfarin Controlled Trials – Warfarin Events per 100 patient-years and HR for Stroke + SE vs comparator

	Q1[1] Event Rate	Q4[2] Event Rate	Q1[1] Hazard Ratio	Q4[2] Hazard Ratio
Active W	1.95	1.47	1.25	2.11
RE-LY	1.92	1.34	0.57	0.95

[1] Q1 = first quartile = quartile with the lowest mean TTR

[2] Q4 = fourth quartile = quartile with the highest mean TTR

Site Mean INR TTR Comparisons

- Better care at sites with higher mean INR TTRs could in part explain lower warfarin arm stroke rates BUT
- It is not likely to explain the effect of warfarin relative to the comparator because improved care should affect both arms equally
- A more likely explanation is that better warfarin control as measured by mean INR TTR results in better outcomes

Methods for Calculating Site TTR

- Method of Connolly: mean = average of TTR values for individual patients
- Method of sponsor: mean = all days of all patients in the therapeutic range divided by total number of days
  - Gives more weight to patients who remain on study drug longer
- Both methods use technique of Rosendaal to impute INR values during days between actual measurements

TTR Data for Hypothetical Site

Patient	Days Treated	Days in Range	TTR
01	1080	756	70%
02	120	60	50%
03	120	60	50%
04	120	60	50%

TTR Data for Hypothetical Site

Patient	Days Treated	Days in Range	TTR	
01	1080	756	70%	
02	120	60	50%	
03	120	60	50%	
04	120	60	50%	
All	**1440**	**936**	**55%**	**65%**
			▲ Connolly TTR	▲ Sponsor's TTR

FDA's Analyses of Site Mean INR TTR

We analyzed site TTR in several ways:

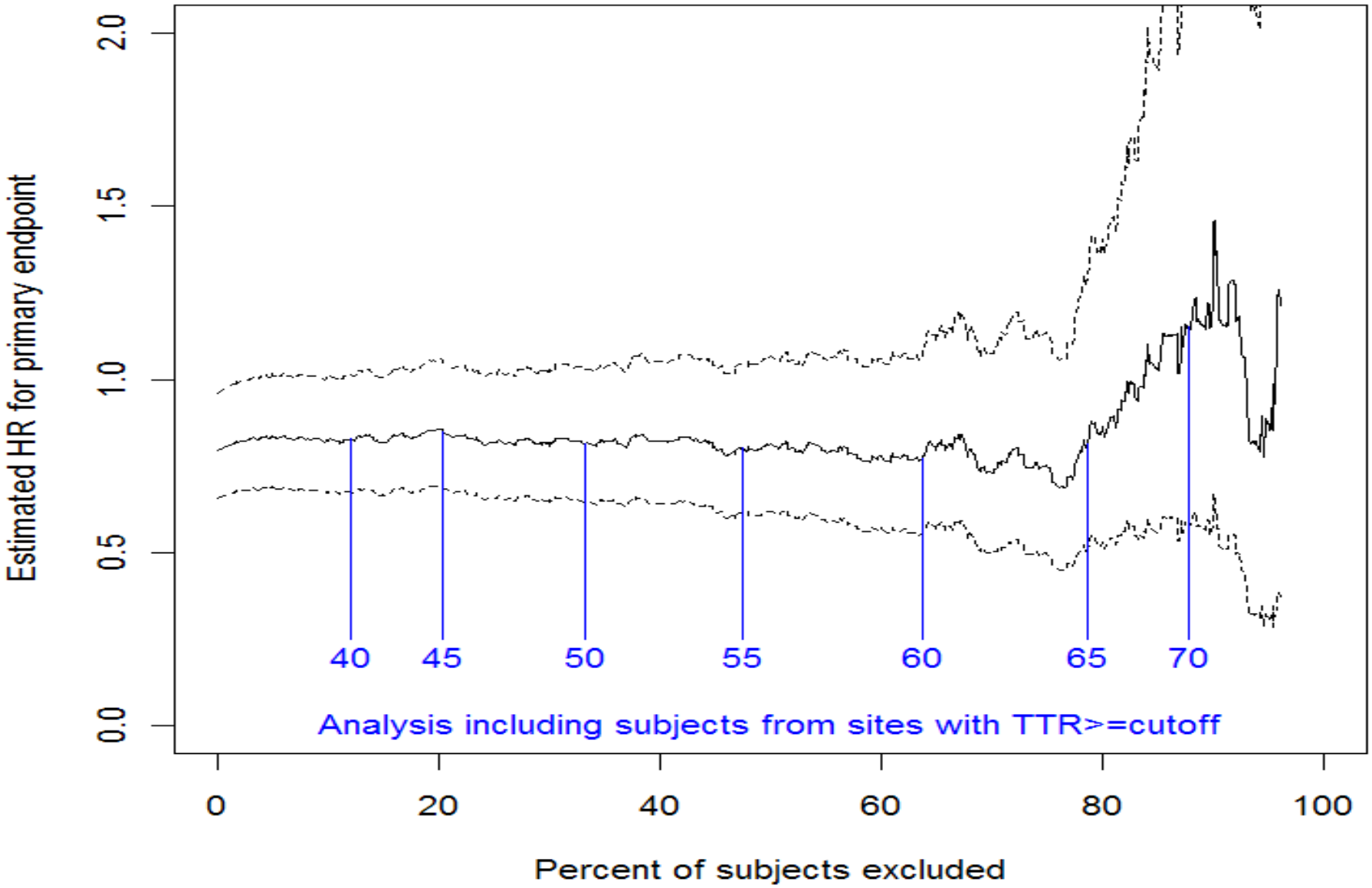
- By subsets based on TTR -
  - By quartiles containing either similar numbers of sites or similar numbers of patients
  - By various TTR cut points
  - As a continuous function of TTR
- By event window -
  - "LD + 2 d" (randomization to last dose + 2 days after VKA discontinued)
  - "LD + 30 d" (randomization to last dose + 30 days)
- All analyses shown are in the Safety Population

FDA's Analysis of Primary Endpoint Results by Site Mean INR TTR

Site Mean TTR	Warfarin		R vs W - Hazard Ratio (95% CI)
	n/N (%)	Events/ 100 pt-yr	
Best Quartile [1] TTR > 63.9 Safety pop, LD + 2 d	55 / 1803	1.75	0.75 (0.49, 1.13)
Best Quartile [2] TTR ≥ 67.8 Safety pop. LD + 2 d	23 / 1165	1.14	1.02 (0.56, 1.84)
TTR ≥ 72.6 Safety pop., LD + 2 d	11 / 623	1.05	1.17 (0.52, 2.65)
Best Quartile [1] TTR ≥ 63.9 Safety pop. LD + 30 d	63 / 1803	1.93	0.98 (0.69, 1.41)
Best Quartile [2] TTR ≥ 67.8 Safety pop. LD + 30 d	29 / 1165	1.38	1.30 (0.79, 2.13)

LD = Last dose
1 Quartiles have similar numbers of patients
2 Quartiles have similar numbers of sites

Hazard Ratio for the Primary Endpoint as a Function of Site Mean INR TTR



Mean INR TTR Quartile Maxima in ROCKET, RE-LY, and Active W

	Upper Limit of TTR in Quartiles[1]		
Study	**Q1**	**Q2**	**Q3**
ROCKET[2]	46.8	55.9	63.9
RE-LY[3]	57.1	65.5	72.6
ACTIVE W[4]	53.8	65.0	73.3

1 Method of Connolly was used to calculate site mean TTR in all rows
2 FDA analysis, quartiles with similar numbers of patients
3 Wallentin L, et. al. Lancet 2010; 376:975-83 (quartiles with similar numbers of patients
4 Connolly SJ, et. al. Circulation 2008; 118:2029-37 (quartiles with equal number of sites)

RE-LY Enrolled many Subjects at Sites with Mean INR TTR > 72.6%

Quartile of site mean TTR		Number of subjects
Q1	<57.1%	N=4510
Q2	≥57.1 to <65.5%	N=4564
Q3	≥65.5 to <72.6%	N=4445
Q4	≥72.6%	N=4505

ROCKET Regional Enrollment and TTR

	% of Patients	TTR (%)
Eastern Europe	38.6	49.7
Asia-Pacific	14.8	52.4
Latin America	13.2	55.2
Western Europe	14.8	60.6
North America	18.8	64.1
Total	**100**	**55.2**

Primary Endpoint Results by Site Mean Time Below Therapeutic Range (TBTR) Quartile

Safety Population, to Last Dose + 2 days – FDA Analysis

Site TBTR (%)	Rivaroxaban		Warfarin		R vs W Hazard Ratio (95% CI)
	N=7061 n/J (%)	Events per 100 pt-yr	N=7082 n/J (%)	Events per 100 pt-yr	
<18.9	37 /1688	1.33	45 /1804	1.47	0.91 (0.59, 1.41)
18.9 - 27.1	59 /1705	2.09	76 /1790	2.56	0.82 (0.58, 1.15)
27.1 - 37.7	48 /1731	1.78	61 /1758	2.22	0.80 (0.55, 1.17)
> 37.7	45 /1764	1.72	60 /1727	2.38	0.73 (0.49, 1.07)

Observed Event Rate as a Measure of Adequacy of Warfarin Administration

- Protocol for ROCKET specified an expected primary endpoint event rate of 2.3%/year in the warfarin arm based on the target population and the observed event rate was in line with the prediction
- Primary event rates in the warfarin arms of SPORTIF III and V were quite different (2.3% vs 1.2%) despite identical eligibility criteria
- The protocol for ROCKET specified an expected event rate of 10%/year for the primary safety endpoint based on the target population– the observed rate was 15%/year

Adequacy of Anticoagulation - Summary

- Increasing levels of site INR TTR are associated with reduced rate of thrombotic events in patients with AF treated with warfarin
- Increasing levels of site INR TTR are associated with changes in the hazard ratio for thrombotic event rates that favor warfarin in warfarin controlled trials of novel anticoagulants
- Site mean TTR is a useful tool to understand the impact of INR control in warfarin controlled studies in patients with AF

Adequacy of Anticoagulation - Summary

- INR control in ROCKET was worse than in other recent trials, potentially biasing the overall results in favor of rivaroxaban
- Few patients were enrolled at sites where warfarin was used skillfully, resulting in insufficient data to assess the efficacy of rivaroxaban compared to warfarin when the latter is used well

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Management of Transition from Study Drug to Warfarin at End of ROCKET

- Sites were encouraged to
  - Start open-label VKA at the expected maintenance dose after the last dose of study drug;
  - Start patients with h/o prior VKA use at their pre-study dose
  - Wait until third day after initiating VKA to get open-label INR
- Bridging with LMWH was allowed

ROCKET - Primary Endpoint Event Rates in Safety Population Following Study Completion

	Rivaroxaban		Warfarin	
Days after last dose	**n/N**	**Events per 100 pt-yr**	**n/N**	**Events per 100 pt-yr**
Days 3-30	**22 / 4637**	**6.2**	**6 / 4691**	**1.7**
3-7	6 / 4637	9.4	1 / 4691	1.6
8-14	7 / 4629	7.9	1 / 4688	1.1
15-30	9 / 4622	4.4	4 / 4687	1.4

J-ROCKET – Primary Endpoint Results – Safety Population

Event Window	Riva n/N (%)	Warfarin n/N (%)
On-treatment (median of 16 months)	11/639 (1.7)	22/639 (3.4)
Completers from day 3 to day 30 after last dose	5/480 (1.0)	1/468 (0.2)

Initiation of VKA After Last Dose of Study Drug in Completing Patients

	Rivaroxaban N=4591	**Warfarin N=4667**
Start day of VKA relative to last day of study drug	n (%)	n (%)
Before last dose	47 (1.0)	61 (1.31)
0- 2 days after	3992 (86.9)	4022 (86.4)
3- 7 days after	144 (3.1)	156 (3.3)
8-30 days after	49 (1.1)	51 (1.2)
>30 days after or never	359 (7.8)	367 (7.9)

Patients Who Completed and Started VKA 0 - 2 Days After Last Dose of Study Drug

	Rivaroxaban N=3992		Warfarin N=4022		
Event Window (Days after last dose)	n	Event Rate /100 Pt-yr	n	Event Rate /100 Pt-yr	Hazard Ratio (95% CI)
Day 2 - 7	4	6.10	1	1.51	4.03 (0.45, 36.1)
Day 2 - 30	17	5.50	6	1.93	2.85 (1.12, 7.23)

Median Time from Last Dose to First INR in Therapeutic Range after Discontinuation of Study Drug in Patients With and Without Primary Endpoint Events

	Riva – W/O Event	Riva – With Event	Warf - W/O Event	Warf - With Event
Completed	4615	22	4685	6
N reaching TR (%)	1624 (35)	10 (45)	3068 (65)	3 (50)
Median (days)	10	8.5	1	6

Comments on Proposed Transition Regimen

- Starting rivaroxaban in patients taking warfarin is not comparable to starting warfarin in patients taking rivaroxaban
- Rivaroxaban may increase INR; discontinuing it at INR ≥ 2 may lead to under-anticoagulation
- The onset of the effect of warfarin is slow
- The time to therapeutic range is not predictable
- INR can fluctuate in and out of the therapeutic range during initiation of therapy
- Concentrations of anti-thrombotic protein C decrease faster than pro-coagulant factors
  - Stopping rivaroxaban too early may result in higher risk of pathologic thrombosis

Post Treatment Events - Summary

- Completing patients in the rivaroxaban arm in ROCKET had a 28 day post treatment stroke rate about 4x that of warfarin arm patients; J ROCKET data are directionally consistent
- The rivaroxaban arm stroke rate was not inconsistent with the observed poor warfarin control in this period, however the data are also not inconsistent with rebound hypercoagulability
- A clinical study may be needed to evaluate rates of bleeding and thrombotic events of the sponsor's proposed strategy for transitioning patients from rivaroxaban to warfarin

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"Reinventing Regulation of Drugs and Medical Devices"

- A notice posted in the Federal Register in 1995 discusses the Agency's standards for demonstrating effectiveness of human drug products.
- This policy document states that in most cases:

  "…a showing of effectiveness is usually based on a clinical trial comparing the product to a placebo. Such a showing does not necessarily involve a comparison to another active treatment or a product that is known to be effective."

"Reinventing Regulation of Drugs and Medical Devices" (cont'd)

But this notice goes on to state:

"In certain circumstances, however, it may be important to consider whether a new product is less effective than available alternative therapies, when less effectiveness could present a danger to the patient or to the public. For example, it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when: (1) The disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack) …."

Source: Federal Register Vol. 60, No. 147, pp 39180-81 (Aug 1, 1995)

Application of Policy to Drugs for Stroke Prevention

DCRP has applied this policy as follows:

- A dose of dabigatran that was clearly non-inferior to warfarin was not approved because it was significantly inferior to a higher dose of dabigatran in terms of stroke rate
- We have stated a NDA for a drug to prevent stroke in AF patients based solely on a trial in which the active comparator was aspirin is not approvable
  - A finding of superiority to aspirin indicates a drug is effective, but warfarin is so much more effective than aspirin that aspirin is not a relevant comparator

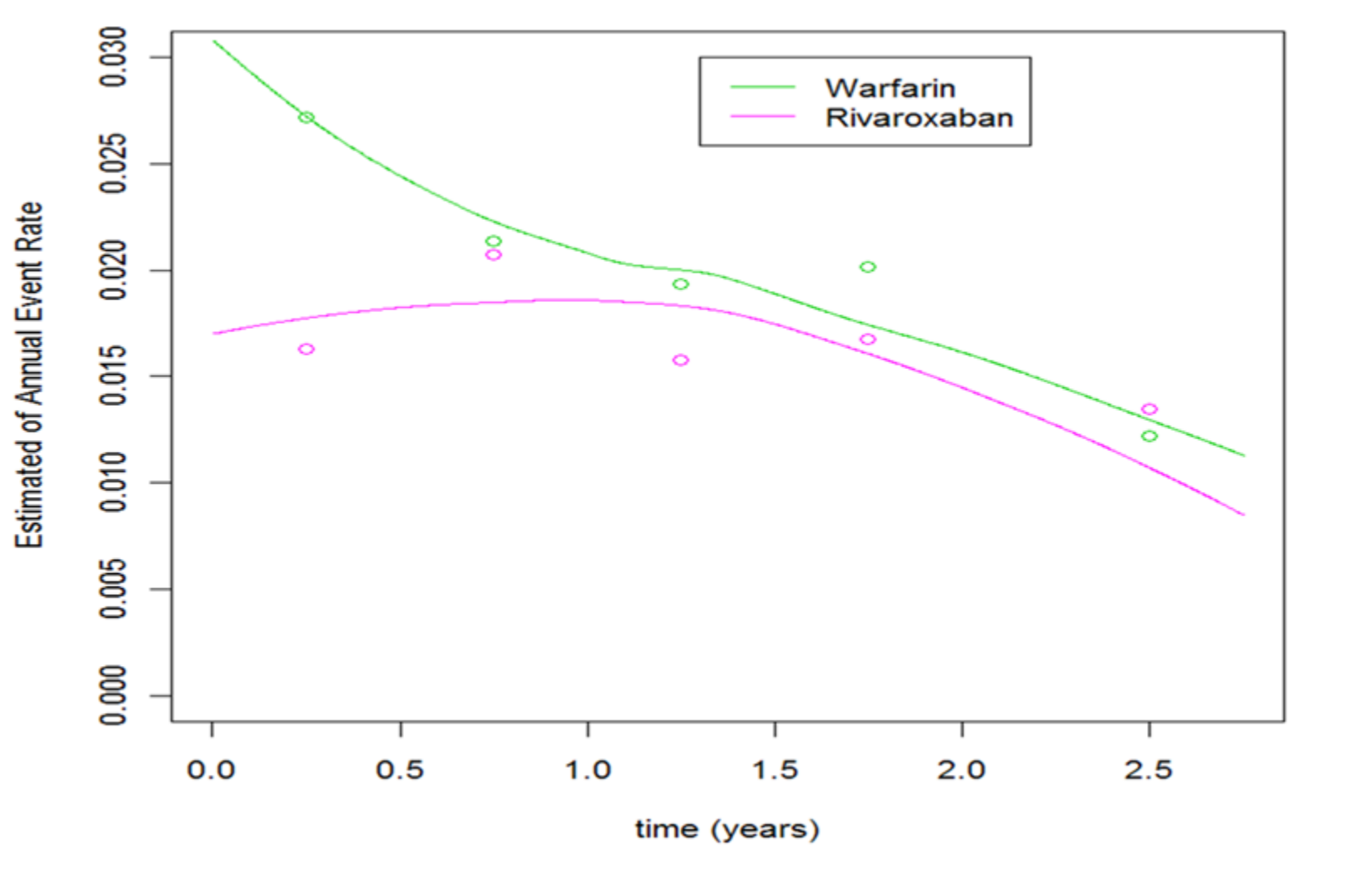
Approval Standard

The 1995 Federal Register notice states a policy without much operational detail. There are unanswered questions:

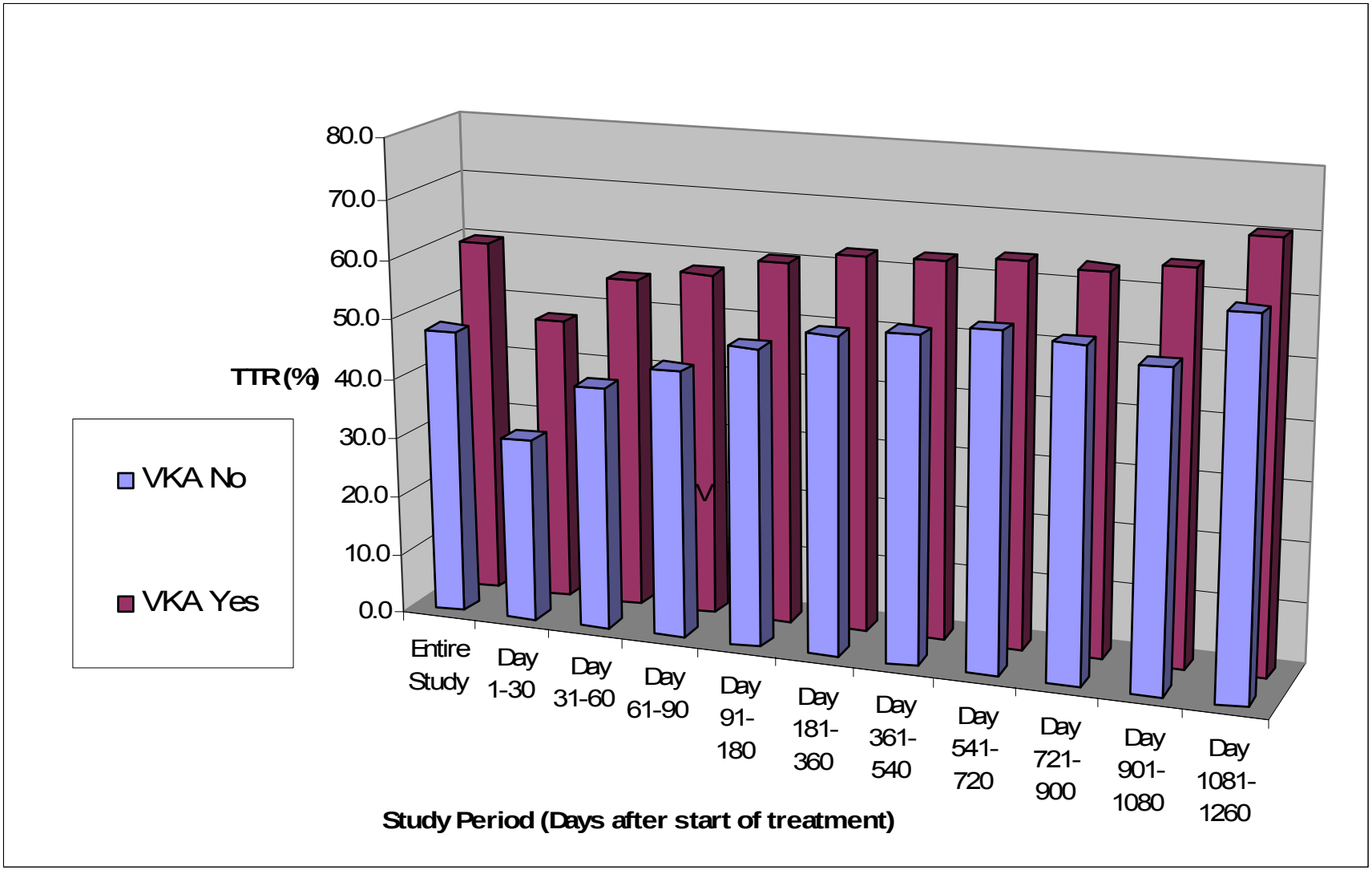
- How much of the comparator's efficacy has to be maintained?
- How much uncertainty about the efficacy results is acceptable?
- What if another treatment for the indication is approved during the course of development?

BACKUP SLIDES

Primary Efficacy Event Rate vs. Time on Study Drug (Safety Population)



Primary Endpoint Results by Baseline VKA Status and Time Period

Population and Time Interval From Randomization (Days)	Warfarin Events per 100 pt-yr	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)
VKA Experienced		
1-180	2.28	0.54 (0.33,0.88)
≥ 181	1.73	0.99 (0.74,1.32)
VKA Naïve		
1-180	3.33	0.71 (0.44,1.16)
≥ 181	2.43	0.71 (0.49,1.03)

Percent Time in Therapeutic Range During Study Intervals by Baseline VKA Status